REMARKS

Applicants thank the Examiner for rejoining former Groups I (Claims 1 and 2) and II (Claims 3-5).

The Claims

Upon entry of this amendment, Claims 1, 3-5, and 8-11 will be pending in this application.

Applicants have amended Claims 1, 3, and 4, and added new Claims 8-11 to clarify the subject matter claimed. Support for these amendments and claims can be found throughout the specification, including the original claims. See, *e.g.*, page 5, the second full paragraph to page 7, the first paragraph; the original Claim 3; and Example 1. Applicants have also canceled Claims 2, 6, and 7 without prejudice. Applicants reserve the right to prosecute claims of identical or similar scope to the original claims in other applications claiming the benefit of this application and its predecessor applications.

The Figures and Specification

The Examiner has objected to the Brief Description of the Drawings for failing to match the drawings filed with this application on December 1, 2000. Specifically, the Examiner states that there is no reference to Figure 5, and there is no Figure 7 despite the reference to "Figure 7" in the Brief Description of the Drawings.

Applicants' agent Yu Lu called the Examiner on June 13, 2005 to clarify the objection. The Examiner confirmed that no new formal drawings are required. Instead, the Examiner directed Applicants to address the objection to the specification on pages 2-3 of the Office Action. Applicants have done so, and amended the Brief Description of the Drawings and other parts of the specification to reflect the Figures actually filed with this application.

In the Brief Description of the Drawings, Applicants have deleted the description of Figure 5 that is part of the same paragraph (page 4) as the description of Figure 4. No such Figure 5 was filed with this application. Figure 5 filed with the application did not depict the recited % survival. Applicants have also amended the numbering of former Figures 6 and 7,

to correctly be Figures 5 and 6, respectively. This numbering is consistent with Figures actually filed with the application.

Consistent with these changes, Applicants have also amended the specification as appropriate to reflect the correct figures.

None of these amendments is new matter. Applicants request their entry, and reconsideration and withdrawal of the objection.

Rejection under 35 U.S.C. § 101

Claims 1-5 stand rejected under 35 U.S.C. § 101 as directed to non-statutory subject matter. Specifically, the Examiner argues that independent Claims 1 and 3 (and their dependant claims) read on genetically altered or transgenic humans, despite the fact that the specification explicitly defines the term "animal" as excluding humans. Applicants traverse.

Although not acquiescing to this rejection because the application specifically excludes human, to advance prosecution, Applicants have amended the pending claims to clarify that the subject matter claimed is not directed to a human, but to a non-human animal – specifically, a mouse.

In view of this amendment, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 101.

Rejection under 35 U.S.C. § 112, first paragraph

(1) Written Description

Claims 1-5 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Examiner argues that the claims contain subject matter that is not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants traverse.

To expedite prosecution and to clarify the subject matter claimed, Applicants have amended Claims 1, 3, and 4, canceled Claim 2, and added new Claims 8-11. Support for these amendments and new claims can be found throughout the specification, including the

original claims. See above.

The Examiner argues that Claims 1 and 2 encompass animals in which Caspase-9 expression is defective in any way, for example, due to "genetic alterations in transcription factors or gene regulation that would lead to an increase or decrease in Caspase-9 expression" (page 4). This rejection is rendered moot by Applicants' amendments. Claim 1 recites that the defective Caspase-9 expression results from a defect in the Caspase-9 gene. Claims 3-5 recite a specific defect, *i.e.*, a QACXG deletion from the coding region of the gene. Thus, the claims no longer encompass transcription or gene regulation factor defects.

The Examiner further argues that "[t]he specification does not contemplate any specific animals with decreased or a total lack of Caspase-9 expression, except Caspase-9 constitutive knock out mice" (page 4). Applicants traverse.

The specification and the original claims have written description that makes it clear that not only a knock-out (*i.e.*, total deficient in function) mouse is contemplated as part of the claimed invention. For example, original Claims 1 and 3, and the first sentence of the DETAILED DESCRIPTION OF THE INVENTION clearly describe animals "defective" in Caspase-9 expression. According to Merriam-Webster Online, "defective" means either "imperfect in form or function," or "falling below the norm in structure or in mental or physical function." Neither requires total lack of function.

It was common knowledge within the art, at the time of filing this application, that there were numerous ways to render a gene (*e.g.*, the Caspase-9 gene) defective. For example, a skilled artisan would immediately envisage that deletion of the ATG start codon of *any* gene would render the gene product defective. The gene product (e.g., encoded protein) would either fail to be translated, or be translated in a wrong reading-frame, or be translated inefficiently from a cryptic start codon, to name but a few possibilities. A skilled artisan would also immediately envisage that inserting polynucleotides into and/or deleting polynucleotides from the coding sequence of *any* gene can predictably cause a frame-shift mutation, anywhere within the gene, thus resulting in a gene product at least partially defective in function. A skilled artisan would further immediately envisage that deleting the TATA box of *any* gene can impair the translation of the transcribed gene, and that changing sequences at the intron-exon junctions can affect gene splicing and mature mRNA

production. Other methods well-known in the art to affect gene expression from a gene are specifically referred to in the specification. See, *e.g.*, page 5, lines 25-31 of the specification.

Pursuant to MPEP 2163, Section II(A)(2): "[t]he analysis of whether the specification complies with the written description requirement calls for the examiner to compare the scope of the claim with the scope of the description to determine whether applicant has demonstrated possession of the claimed invention. Such a review is conducted from the standpoint of one of skill in the art at the time the application was filed (see, *e.g.*, *Wang Labs. v. Toshiba Corp.*, 993 F.2d 858, 865, 26 USPQ2d 1767, 1774 (Fed. Cir. 1993)) and should include a determination of the field of the invention and the level of skill and knowledge in the art. Generally, there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement. Information which is well known in the art need not be described in detail in the specification. See, *e.g.*, *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379-80, 231 USPQ 81, 90 (Fed. Cir. 1986)."

At the filing date of this application, the level of skill and knowledge in the gene expression and modification art was very high, particularly in the context of genetically altering the expression level of a known gene (*e.g.*, Caspase-9). Thus, there was no need to describe such different genetic alterations in detail in the specification. Applicants have thus provided adequate written description for a representative species of defective Caspase-9 gene.

The Examiner also argues that the specification fails to identify any Caspase-9 sequences (including genomic DNA sequences) belonging to animal species other than mouse. Applicants do not acquiesce in the Examiner's reasoning, or agree to the contention or suggestion that other Caspase-9 sequences were not known at the time the application was filed even now. These other Caspase-9 sequences can also be easily used in this claimed invention. Nevertheless, solely to advance prosecution, Applicants have amended the claims to recite mouse. This overcomes the rejection.

In rejecting Claims 3-5 for lack of written description, the Examiner argues that the only mouse sequence illustrated in the specification is that in Example 1 (page 8). Applicants traverse.

The illustrative sequence of Example 1 was obtained from a 129SV/J genomic library using a human Caspase-9 cDNA. Plainly, the exact same technique would allow isolation of other mouse Caspase-9 genomic clones. Alternatively, the mouse clones isolated in Example 1 could be used to isolate other mouse sequences. Neither approach would require any undue experimentation, or generate polynucleotides with many sequence variations. Thus Applicants have described a genus of mouse Caspase-9 genes.

Caspase-9 gene sequences from different mice strains are very likely to be nearly identical to one another, if not completely identical. It is almost certain that the Caspase-9 gene described in the instant specification can hybridize under high stringency condition to *any* other mouse Caspase-9 gene, thus constituting a representative species under the "Revised Interim Written Description Guidelines Training Materials" (see Example 9 therein, regarding a single representative species of polynucleotide meeting the written description requirement for a claimed genus of polynucleotides capable of hybridizing under stringent condition to the disclosed species).

Because all of the mouse Caspase-9 genes are likely to be almost identical, it would also be expected that a mouse Caspase-9 without the QACXG motif, as claimed in Claim 3, would be defective, irrespective of what other mouse sequence variations might distinguish the two mouse Caspase-9 genes.

For all of the above reasons, and in view of Applicants' claim amendments, Applicants respectively request that the Examiner reconsider and withdraw the § 112, first paragraph, written description rejection.

(2) Enablement

Claims 1-5 stand rejected under 35 U.S.C. § 112, first paragraph, for failing to enable a skilled artisan to practice the invention commensurate in scope with the claims. Applicants traverse.

The Examiner argues that the claimed invention is not enabled because it encompasses transgenic gain-of-function animals, total or conditional Caspase-9 knock-out animals, or transgenic animals expressing increased level of negative Caspase-9 regulators. Citing Wall and Houdebine, the Examiner further contends that the state of the art of

transgene expression to achieve a desired phenotype is unpredictable.

Not acquiescing in the reasoning or agreeing to the assertions of the Office Action, and solely to advance prosecution, Applicants, as described above, have amended the claims to clarify that the defect in Caspase-9 expression results from a defective Caspase-9 gene. This renders the Examiner's concern about transgenic animals expressing Caspase-9 regulators moot.

Regarding conditional knock-outs, the Examiner cites Leneuve as supposedly providing evidence of his contention that "the making of conditional knock-outs remains unpredictable even in mouse." Leneuve provides no such evidence. It is a research article teaching an improved method of generating conditional knock-out mice. Thus the Examiner's citation of a background sentence is out of context and does not reflect the teaching of Leneuve. According to Leneuve, the presence of the LoxP sites *may*, but does not necessarily, affect the expression of a target gene. Thus, removing such sequences is merely *recommended*, not mandatory, for the technique to work. Even in those situations where the loxP sites do need to be removed, there are many techniques routinely available for doing so (see, *e.g.*, Ref. 9, Gschwind and Huber, *Mol. Cell. Biol.* **18**: 4651-58, 1998; or Ref. 11, Tronche et al., *Nature Genet.* **23**: 99-103, 1999, cited at the end of Leneuve). These techniques are different from the tri-lox technology, and there is no evidence that these techniques are not as "straightforward" as the tri-lox method is.

The Examiner also asserts that the specification does not teach parts of the Caspase-9 gene other than the QACXG sequence that can be knocked-out by homologous recombination. However, as explained above, at the filing date of this application, a skilled artisan understood that there were myriad ways to make a known gene defective, such as deletion of the coding sequence or important parts thereof. See also, page 5, lines 25-31 of the specification. "A patent need not teach, and preferably omits, what is well known in the art." (MPEP 2164.01).

The Examiner further alleges that the specification does not teach that the Caspase-9 gene knock-out will produce the same phenotype in any mouse strain other than C57BL/6 strain. Applicants traverse.

The Examiner had confused *phenotype* with *genotype*. The claims do not contain any limitations on particular phenotypes other than gene expression, which is directly linked to genotype. If the Caspase-9 gene is defective, the encoded protein, if any is produced at all, is intrinsically defective, regardless of the genetic background of the mouse strain in which such defective protein is expressed (if expressed at all). Even if different mouse strains may give rise to different phenotypes (which Applicants do not concede), such variation in phenotypes is irrelevant to the claimed invention. A skilled artisan need not produce any particular phenotype in order to practice the claimed invention.

In fact, once one strain of a claimed mouse defective in Caspase-9 expression is generated, the defective Caspase-9 gene can be back-crossed into a different strain of mouse through routine breading and genotyping. Both techniques are well-known and routinely practiced within the art. No undue experimentation is needed to generate a different strain of mouse from one strain of Caspase-9 defective mouse.

In view of the above arguments and claim amendments, Applicants respectively request that the Examiner reconsider and withdraw the enablement rejection under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. § 112, second paragraph

Claim 3 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner points out that the term "arginine of glycine" is unclear. Applicants thank the Examiner for pointing out this obvious typographic error.

Applicants have amended Claim 3 to correct this error. The specification as filed supports this amendment. See, for example, the sequence listing filed with the original specification (which refers to "X" as "arginine or glycine," emphasis added).

Applicants have also amended Claim 3 to correct another obvious typographic error: the spelling of "blasotcyst" to "blastocyst." Applicants have also inserted "SEQ ID NO: 7" after the pentapeptide QACXG. None of these amendments are new matter, and do not narrow the scope of Claim 3.

In view of these amendments, Applicants respectfully request reconsideration and withdrawal of the rejection.

CONCLUSION

In view of the foregoing amendments and arguments, Applicants respectfully request reconsideration and withdrawal of the pending rejections. Any questions arising from this submission may be directed to the undersigned at (617) 951-7000.

If there are any other fees due in connection with the filing of this submission, please charge the fees, or credit any overpayment of the same, to our **Deposit Account No. 18-1945**, under the charge number **VPI/98-104 CIP CON US**.

Dated: August 29, 2005

Respectfully submitted,

By_____

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